Request for Continuing Review of IRB-Approved Protocol

Use this form to submit a protocol for continuing review by a CDC IRB or a non-CDC IRB. [See 45 CFR 46.109(e).] See *HRPO Guide: IRB Review Cycle* for further details on how to complete this form.

1 Protocol identifiers

CDC protocol ID: 2087 Protocol version number 38 version date 11/2013

Protocol title: Centers for Birth Defects Research and Prevention (CBDRP)

2 Key CDC personnel

☐ **No change** in key CDC personnel. If no changes, please list only the primary contact and principal investigator.

	Name and degrees (FirstName LastName, Degrees)	User ID	SEV #	CDC NC/division
Primary contact (required)	Kim Newsome	kan3	19773	CDC/NCBDDD/BDDD
Principal investigator (required)	Jennita Reefhuis	nzr5	8753	CDC/NCBDDD/BDDD
Investigator 2				
Investigator 3				
Investigator 4				
Investigator 5				

SEV # is CDC's Scientific Ethics Verification Number. CDC NC/division is the national center (or equivalent) and division (or equivalent), or coordinating center or office if submitted at that level.

List all other CDC investigators, if any. Include name and degrees, user ID, SEV #, CDC NC/division:

3 CDC's research partners

Research partners include *all* direct and indirect recipients of CDC funding (e.g., grants, cooperative agreements, contracts, subcontracts, purchase orders) and other CDC support (e.g., identifiable private information, supplies, products, drugs, or other tangible support) for this research activity, as well as collaborators who do not receive such support. On continuing review, HRPO needs current information on partners that have been added or dropped since the last review and partners that, as of the last review, were receiving support for nonexempt research. See *HRPO Guide: CDC's Research Partners* for further details. Check one of the following.

☐ No research partners are reported with this submission. (This may occur because there are no partners, or because no partners are being added, or because no previously reported partners are still both supported by CDC and engaged in nonexempt research.)

☒ Research partners are listed on form 0.1370, which accompanies this form.

4 Study participants—cumulative demographic frequencies

Have any participants been enrolled in the last 12 months? ☒ yes ☐ no

Report estimated counts (rather than percentages). Include participants at domestic and foreign sites. See *HRPO Guide: IRB Review Cycle* for definitions.

Number of participants	45,358
Location of participants	
Participating at domestic sites	45,380
Participating at foreign sites	0
Sex/Gender of participants	
Female	100
Male	0
Sex/gender not available	0
Ethnicity of participants	
Hispanic or Latino	10,155
Not Hispanic or Latino	35,225
Ethnicity not available	0
Race of participants	
American Indian or Alaska Native	150
Asian	364
Black or African American	4,933
Native Hawaiian or Other Pacific Islander	0
White	26,991
More than one race	2,287
Race not available	0

Comments on demographics

5 Study status—participant involvement

5.1 Contact status

"Contact" means intervention or interaction with participants, such as recruitment, screening, obtaining consent, enrollment, and collection of data and biological specimens directly from participants. Check one of the following.

☐ Study is not designed to involve research-related contact with participants (e.g., research using existing records); study activities involve only access to or analysis of data or biological specimens and writing reports.

☒ Study is designed to involve contact with participants. Check one of the following:

- ☐ Contact with participants has not yet begun.
- ☒ Contact with participants has begun and continues; this may include follow-up for debriefing or notification of results.
- ☐ Contact with participants is completed; study activities involve only data analysis or report writing.

5.2 Consent status

"Consent" includes adult consent, child assent, and parental permission. Check one of the following.

☐ The IRB previously waived all requirements both to obtain and to document consent in this study.

☐ Although not waived, there is no further need to obtain or document consent (e.g., enrollment is complete).

☒ Participants will be asked to provide consent (with or without documentation).

If you check the third box, please include all current consent, assent, and parental permission materials (e.g., scripts, documents) from each study site with this submission.

6 Study status—overall conduct

Summary of research activities to date. Briefly summarize study progress and interim findings. Include the number of potential subjects who declined enrollment and the number who withdrew from the study. If this study involves a registrable clinical trial, summarize registration status.

The Centers for Birth Defects Research and Prevention (CBDRP) collaborate to conduct the National Birth Defects Prevention Study (NBDPS) and the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS). NBDPS ceased interviewing on March 31, 2013; data analyses are ongoing. The Birth Defects Prevention Study BD-STEPS interviews will begin interviewing in February 2014. Both BD-STEPs and NBDPS are case-control studies of major birth defects that include cases identified from existing birth defect surveillance registries across the United States (including metropolitan Atlanta). Centers in nine states participated in NBDPS (AR, CA, GA, IA, MA, NC, NY, TX and UT); all Centers except TX and UT will participate in BD-STEPS. For both studies, control infants are randomly selected from birth certificates or birth hospital records. Mothers of case and control infants are interviewed using a computer-assisted telephone interview. Also for both studies, parents are asked to collect biologic material from themselves and their infants for DNA testing. Information gathered from both the interviews and the DNA specimens will be used to study genetic and environmental factors as well as gene-environment interactions for a broad range of carefully classified birth defects.

As of November 2013, 47,597 cases and 18,269 eligible NBDPS controls have been ascertained in the nine states. Interviews have been completed with 32,016 NBDPS eligible case and 11,741 eligible control mothers. The current case participation rate for the interview was 66% and 58% for the cheek cell collection. A total of 25,281 NBDPS mother, 21,292 father and 22,880 infant samples have been received to-date.

A comprehensive research agenda of more than 200 proposed projects has been developed for analyzing the compiled interview, clinical and biological data. The NBDPS analytic database version 9 contains 27,809 cases and 10,200 controls, providing a large enough sample size for analysis for many of the proposed projects.

The NBDPS is current with Georgia DHR IRB. All Centers have up-to-date local IRB approval. The Centers are in the process of either submitting paperwork for IRB deferral to CDC IRB or submitting an IRB amendment for BD-STEPS. All current approval notifications are attached.

Summary of study changes reviewed and approved since the last continuation. Do not include changes submitted with or before approval of this continuation but not yet approved.

Modification 1: ADDED RESEARCH PARTNERS - Approved January 11, 2013

We added research partners as noted in 1370. This Amendment is submitted at the same time as the IRB Continuation for this project.

Modificatin 2: CONSENT WAIVER - Approved January 31, 2013

The protocol has been modified by adding an explanation of the waiver of consent. This is reflected on page 53, section 5.B., Written Informed Consent for Genetic Research.

Modification 3: GENE ONE PAGERS - Approved June 27, 2013

As described in the NBDPS protocol, approval of candidate genes to be studied in the NBDPS is an ongoing process. When NBDPS scientists wish to study a new gene, a one-page description of the gene is submitted to the CDC IRB. The review is expedited as this will be an ongoing process throughout the study. In cases of birth defects involving structural malformations of the newborn (including but not limited to NTDs), we propose to study the the presence of polymorphisms located in the following genes: Rho GTPase activating protein 31 (ARHGAP31) gene; the MCM6 (minichromosome maintenance proteins 6) gene; the ataxin-2 (ATXN2) gene; the inducible T-cell co-stimulator (ICOS) gene. In addition, we propose to study the presence of 28 SNPs associated with celiac disease in cases of birth defects involving structural malformations of the newborn, including but not limited to neural tube defects. Descriptions of these genes and justification are described in the attached documents.

Modification 4: BD-STEPS Change in defects studied - Approved August 8, 2013

Although NBDPS ascertained 30 birth defects, BD-STEPS will focus on a subset of these. Infants are eligible for inclusion in BD-STEPS if they have one or more defects from the list of 17 birth defects included in Attachment 5. In addition to selecting birth defects with unknown or uncertain etiology, these defects were selected for the following reasons; the defect is considered to be a major defect (affecting survival, requiring substantial medical care, or resulting in marked physiological or psychological impairment); the defect is usually identifiable in the first six weeks of life; and the defect is consistently ascertainable and classifiable. See protocol pages 16-17 for description of BD-STEPS case defintion.

Modification 5: BD-STEPS Change in Questionnaire Questions - Approved August 8, 2013

A large portion of the BD-STEPS interview will be maintained from the NBDPS to make pooling of the CBDRP's NBDPS and BD-STEPS data possible; pooled data will facilitate the analysis of rare exposures and the examination of trends over time. While the BD-STEPS interview instrument contains many of the same sections,innovative questions have been added in response to some of the findings from NBDPS and in the literature. Changes include shortening the interview, adding questions about maternal diseases, and expanding sections to provide increased detail (e.g. indication and dose for specific medications). See protocol pages 27-28 for full description of the interview questions. The new questionnaire is included as Attachment 18.

Modification 6: BD-STEPS Centralized Interview - Approved August 8, 2013

BD-STEPS interviewing for all the sites will be done by one central CDC-funded contract interviewing facility, which will increase consistency and efficiency. Contact information for the subjects will be encrypted and sent from the individual CBDRP to the interviewing facility via the CDC provided secure SAMS (Secure Access Management Services) system. Interviews will be conducted via the telephone using a system that allows eligible participants to see a local phone number displayed on their caller ID display for each of the sites (Voice over Internet Protocol, VoIP). See protocol page 26.

Modification 7: BD-STEPS Genetic data collection - Approved August 8, 2013

Genetic data collection will be collected from saliva in BD-STEPS instead of cheek cells for NBDPS. All amended genetic collection materials are included as attachment 25-32.

Modification 8: BD-STEPS Collaborating Centers - Approved August 8, 2013

Collaborating Centers for BD-STEPS will most likely be a subset of the NBDPS Centers participating in NBDPS data collection. While existing NBDPS Centers will continue to participate in data analyses, it is expected that not all NBDPS Centers will collect new data as part of BD-STEPS. When Centers are named, an amendment will be submitted with named Centers; new partners will be added using Form 1370 if needed at this time.

Modification 9: BD-STEPS Medical Records - Approved August 8, 2013

At the end of the interview, requests will be made of participants with certain procedures/conditions for mailing an additional consent for medical/dental records. Medical records contain specific information that might be hard for women to recall, and medical record review allows validation of exposures reported by the mother in the

questionnaire. Initial topics for which medical records will be requested include fertility treatments and dental treatments. Complete study materials for collection of medical records are described on page 28 of the protocol and included as attachments 19-22.

Modification 10: BD-STEPS Consent Addition - Approved August 8, 2013

The written consent for saliva samples contains a new section, "Sharing your genetic and health information for future research," that was not in the previous NBDPS written (genetics) consent. This section was added because of a new NIH GWAS policy that requires data from NIH-supported GWAS to be deposited into the NIH GWAS data repository, currently designated as the database of Genotypes and Phenotypes (dbGaP). See p. 3 of the consent (Attachment 26) for additional language that describes how these data will be potentially shared.

Summary of any recent literature or other information relevant to the research study (not limited to information with CDC co-authorship).

Over 180 manuscripts using NBDPS pooled data have been published as of November 2013 with over 20 additional papers under review or in press. Over 300 oral presentations or abstracts have been presented as well. See attached publication list 'NBDPS Publications' for more details.

Summary of all adverse events to date. In particular, address adverse events that were serious, unexpected (or more frequent or severe than expected), or at least possibly related to the research.

None

Summary of (a) incidents that are not adverse events and (b) other substantial concerns since last continuation.

None

List and include copies of progress or monitoring reports on safety or compliance (e.g., site monitor, safety review, DSM report, multi-center trial report, but not reports to PGO).

Summary of remaining research activities, emphasizing future contact with subjects, use of identifiable private data and biological specimens, and preparation of primary reports.

The CBDRP will continue to analyze NBDPS data in the upcoming year. BD-STEPS will focus on data collection for the upcoming year and until the data are clean and ready to be analyzed. Future analyses will include NBDPS only data analyses, BD-STEPS and NBDPS combined data analyses, and BD-STEPS only data analyses.

An increasing number of manuscripts are being submitted for publication, and NBDPS and BD-STEPS findings will continue to be reported to the scientific community for many years (see 'publications' attachment).

7 Regulation and policy

7.1 Mode of IRB review on CDC's behalf

Location of IRB (check one):

☒ CDC IRB

☐ Non-CDC IRB through IRB authorization agreement [submit form 0.1371 if this is a new request]

Institution or organization providing IRB review: _____

IRB registration number (if known): _____

Federalwide assurance number (if any): _____

IRB-determined level of risk to subjects (check one):

☒ Minimal

☐ Greater than minimal

Suggested level of IRB review (check one):

See *HRPO Worksheet for Expedited Review* for detailed assistance. If relying on a non-CDC IRB, please indicate the level of review that you think is appropriate under human research regulations.

☐ Convened-board review is suggested

Reason for convened review: _____

☒ Expedited review is suggested, under the following categories (check all that apply):

- ☐ 1a Study of drugs not requiring Investigational New Drug exemption from FDA
- ☐ 1b Study of medical devices not requiring Investigational Device Exemption from FDA
- ☐ 2a Collection of blood from healthy, nonpregnant adults; below volume limit, minimally invasive
- ☐ 2b Collection of blood from other adults and children; below volume limit, minimally invasive
- ☒ 3 Prospective noninvasive collection of biological specimens for research purposes
- ☐ 4 Collection of data through routine, noninvasive procedures, involving no general anesthesia, sedation, x-rays, or microwaves
- ☐ 5 Research that uses materials collected solely for nonresearch purposes
- ☐ 6 Collection of data from voice, video, digital, or image recordings made for research purposes
- ☒ 7 Research that uses interview, program evaluation, human factors, or quality assurance methods

Continuing review of research previously approved by the convened IRB where

- ☐ 8a the research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects
- ☐ 8b no subjects have been enrolled and no additional risks have been identified
- ☐ 8c the remaining research activities are limited to data analysis

- ☐ 9 Continuing review of research, not under IND/IDE, where categories 2 through 8 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified

8 Material submitted with this form

Check all that apply. Describe additional material in the comments section. Required items are indicated. Optional items may be requested by HRPO or the IRB.

☒ Complete protocol (required if research poses more than minimal risk to subjects, is under IND/IDE, or has changed in the past 12 months)

☒ Consent, assent, and permission documents or scripts (required if consent will be sought in the future from prospective subjects or their representatives [see section 5.2])

☒ Other information for recruits or participants (e.g., ads, brochures, flyers, scripts; required if consent will be sought in the future from prospective subjects or their representatives)

☒ Data collection instruments (e.g., questionnaires, interview scripts, record abstraction tools; required if protocol has changes in the past 12 months)

☒ Certification of IRB approval or exemption for research partners (required only for partners being added or for supported/nonexempt partners)

☐ Progress and monitoring reports (recommended when available)

9 Additional comments

None